REMARKS / ARGUMENTS

Support for Amendments

Amendments to the claims are supported throughout the application as originally filed including the original specification and drawings. Specific passages are provided in support of each amendment.

Claim 1 is amended to recite the at least two electrode structures are positioned on the same plane and have substantially the same surface area. Support may be found in paragraph [0131], which recites, "As used herein, "at least two electrodes fabricated to a same plane of said substrate" means that, if the nonconducting substrate has multiple layers, the at least two electrodes are fabricated to the same layer of the substrate." Support may further be found in Figure 1A, 1B, 1C, 2, 3, 4A, 4B, 5, 6, 7A-7F, 12A-12C, 13B-13C, 14B-14C, 15A-B, 18, 22, 23, 24, 25 where the electrode structures in each of these figures are located on the same plane. Further support may be found in paragraph [0132], which recites in part,

> As used herein, "said . . . electrodes have substantially same surface area" means that the surface areas of the electrodes referred to are not substantially different from each other, so that the impedance change due to cell attachment or growth on any one of the electrodes referred to will contribute to the overall detectable change in impedance to a same or similar degree as the impedance change due to cell attachment or growth on any other of the electrodes referred to."

Further support may be found in paragraph [0036], which recites in part " Figure 1A is a schematic representation of a device 100 with two electrode structure of same or similar areas deposited on a substrate". Support may further be found in Figure 1A, 1B, 1C, 2, 3, 4A, 4B, 5, 6, 7A-7F, 12A-12C, 13B-13C, 14B-14C, 15A-B, 18, 22, 23, 24, 25 where the electrode structures in each of these figures have substantially same surface area.

Claim 1 is also amended to recite the electrode element width is between 1.5 and 15 times the width of the electrode gap between electrode elements of different electrode

structure with each said electrode array. Support may be found in paragraph [0172], which recites in part,

> "Where an electrode gap is not of rectangular geometry, "electrode gap" refers to the averaged dimension of the gap that extends in the plane of the substrate (in the direction normal to the major axis of the gap) from where it borders one electrode element to where it borders the other electrode element on its opposite side."

Support may further be found throughout the application, where "electrode gap" or "gap" is always followed by the "between electrode elements" or "between electrodes". For example, support may be found in paragraph [00175], which recites in part, "In the present application, it is preferred that the electrode gap between electrode elements should be designed with respect to the electrode width".

Claim 1 is also amended to recite cell attachment or growth results in cellular contact with at least one of said electrode structures further resulting in a detectable change in AC electrical impedance. Support may be found in paragraph [0080], which recites in part, "Electrode structures on the substrate were used to measure impedance changes following cell attachment to the electrode surfaces to monitor cell attachment and/or growth in the wells (or fluidic containers)." Further support may be found in paragraph [00134], which recites in part, "Alternatively, the impedance change refers to the difference in impedance values when cells are attached to the electrode surface and when cells are not attached to the electrode surface, or when the number, type, activity, or morphology of cells attached to the electrode-comprising surfaces of the apparatus changes. .... In addition, impedance has two components, resistance and reactance...". Further support may be found in paragraph [0227], which recites in part, "The external impedance analyzer or impedance measuring circuits are then used to connect these connection pads for the measurement of electrical impedance." Further support may be found in paragraph [00155], which recites in part, "For example, impedance can be measured in a frequency ranging from about 1 Hz to about 100 MHz". Here the impedance is AC electrical impedance in a frequency ranging from about 1 Hz to about 100 MHz. Further support may be found in Figures 26A, 26B, 27, 28, 29, 31, 32, 34, 35,

36, 37, 38, 39, 40, 41, 42A, where resistance and reactance shown are AC electrical impedance components.

Claims 1, 37, 38 and 43 are amended to refer to target cells and thus to reduce fees associated with additional dependent claims directed towards molecules.

Claim 10 is amended to recite the at least two electrode elements comprise a plurality of electrode elements, further wherein the plurality of electrode elements of different electrode structures are evenly spaced. Support may be found in paragraph [0030], which recites in part, "Each electrode array may include a plurality of evenly spaced electrode pairs." Further support may be found in paragraph [0036], which recites in part, "Electrode structures 210 and 220 comprise multiple interconnected electrode elements."

Claim 12 is amended to recite each array is organized so that electrode elements have a geometry selected from the group consisting of circle-on-line, diamond-on-line, concentric, sinusoidal, interdigitated or castellated fashion. Support may be found on paragraph [00147], which recites in part, "Non-limiting examples of electrode geometries include interdigitated electrodes, circle-on-line electrodes, diamond-on-line electrodes, castellated electrodes, or sinusoidal electrodes."

Claim 13 is amended to correct dependency.

Claim 21 is amended to clarify the electrode elements of each array are of equal widths. Support may be found in paragraph [0029], which recites in part, "The electrodes of each electrode array may be of equal widths."

Claim 24 is amended to correct dependency.

Claim 37 is amended to recite one or more capture reagents immobilized on the surfaces of at least two electrode structures in each electrode array. Support may be found in paragraph [0034], which recites in part, "In a preferred embodiment, the device

includes one or more capture reagents immobilized on the surfaces of at least two electrodes in each electrode array."

Claim 38 is amended to recite that change in impedance occurs between or among electrode structures and a detectable change in impedance is indicative of attachment of the cells on the surface of the one or more electrode arrays. Support may be found in paragraph [00153], which recites, "Preferably, cell attachment or growth on the surface of any of the electrodes or electrode structures in the above devices results in detectable change in impedance between or among said electrodes or electrode structures."

Claim 43 is amended to recite target cells are attached on an electrode surface. Support may be found in paragraph [00153], which recites, "Preferably, cell attachment or growth on the surface of any of the electrodes or electrode structures in the above devices results in detectable change in impedance between or among said electrodes or electrode structures."

Claim72 is amended to recite the at least two electrode structures are fabricated to the same side and plane of said substrate and cell attachment or growth on any of said at least two electrode structures results in detectable change in AC electrical impedance between or among the electrode structures. In addition, the gap referred to is the gap between electrode elements of different electrode structures.

Support may be found in paragraph [0131], which recites, "As used herein, "at least two electrodes fabricated to a same plane of said substrate" means that, if the nonconducting substrate has multiple layers, the at least two electrodes are fabricated to the same layer of the substrate." Support may further be found in Figure 1A, 1B, 1C, 2, 3, 4A, 4B, 5, 6, 7A-7F, 12A-12C, 13B-13C, 14B-14C, 15A-B, 18, 22, 23, 24, 25 where the electrode structures in each of these figures are located on the same plane.

Support may also be found in paragraph [0080], which recites in part, "Electrode structures on the substrate were used to measure impedance changes following cell attachment to the electrode surfaces to monitor cell attachment and/or growth in the wells (or fluidic containers)." Further support may be found in paragraph [00134], which

recites in part, "Alternatively, the impedance change refers to the difference in impedance values when cells are attached to the electrode surface and when cells are not attached to the electrode surface, or when the number, type, activity, or morphology of cells attached to the electrode-comprising surfaces of the apparatus changes. .... In addition, impedance has two components, resistance and reactance...". Further support may be found in paragraph [0227], which recites in part, "The external impedance analyzer or impedance measuring circuits are then used to connect these connection pads for the measurement of electrical impedance." Further support may be found in paragraph [00155], which recites in part, "For example, impedance can be measured in a frequency ranging from about 1 Hz to about 100 MHz". Here the impedance is AC electrical impedance in a frequency ranging from about 1 Hz to about 100 MHz. Further support may be found in Figures 26A, 26B, 27, 28, 29, 31, 32, 34, 35, 36, 37, 38, 39, 40, 41, 42A, where resistance and reactance shown are AC electrical impedance components.

Support for the gap being positioned between electrode elements of different electrode structures may be found in paragraph [0172], which recites in part, "Where an electrode gap is not of rectangular geometry, "electrode gap" refers to the averaged dimension of the gap that extends in the plane of the substrate (in the direction normal to the major axis of the gap) from where it borders one electrode element to where it borders the other electrode element on its opposite side."

Claim 290 is newly added and recites the electrodes's elements widths are between about 0.5 times and 10 times the size of the cells used. Support may be found in paragraph [00174], which recites in part, "Preferably, an electrode element's width is between about 0.5 times and about 10 times the size (e.g., the width of an average cell when it spreads and attaches to the substrate) of cells used in an assay that uses the device."

Claim 291 is newly added and recites the electrode elements' widths are in the range between 20 micron and 500 micron. Support may be found in paragraph [00175], which recites in part, "More preferably, the electrode width is in the range between 20 micron and 500 micron."

Claim 292 is newly added and recites the gap between electrode elements of different electrode structures ranges from 0.2 time to 3 times the width of an average cell used. Support may be found in paragraph [00173], which recites in part, "While other gap dimensions may be used, preferably, the gap between electrode elements of the electrode structures ranges from about 0.2 times and 3 times the width of an average cell used in an assay using the device."

Claim 293 is newly added and recites that the gap between the electrode elements of different electrode structures is between 3 micron and 80 microns. Support may be found in paragraph [00173], which recites in part, "Preferably, the width of a gap between electrodes or electrode elements of a device of the present invention used for monitoring eukaryotic cells, such as mammalian cells, such as cancer cells, endothelial or epithelial cells, is between about 3 microns and 80 microns."

Claim 294 is newly added and recites that the electrodes comprise one or more materials selected from the group consisting of indium tin oxide (ITO), chromium, gold, copper, nickel, platinum, silver, titanium, steel and aluminum. Support may be found in paragraph [00177], which recites in part, "Non-limiting examples of materials for electrodes or electrode elements are indium tin oxide (ITO), chromium, gold, copper, nickel, platinum, silver, steel, and aluminum."

Claim 295 is newly added and recites that the electrodes can be optically active. Support may be found in paragraph [00179], which recites in part, "Alternatively, optically-transparent electrodes can be used in a device of the present invention so that the electrodes can not only monitor molecular reactions (and cell substrate impedance) but also permit optical evaluation and inspection of sample solutions under an optical microscope of any kind or by other optical detection means."

Claim 296 is newly added and recites the surfaces of the electrode structures are modified with a cell-adhesion promotion moiety. Support may be found in paragraph

[0077], which recites, "Figure **23** is a schematic representation of an apparatus where the electrode surface has been modified with molecules that promote cell adhesions." Further support may be found in paragraph [00154], which recites in part, "Preferably, an electrode having a smaller surface area than the largest electrode of said at least two electrodes has a surface modified by a cell adhesion-promoting moiety."

Claim 297 is newly added and recites the cell adhesion promotion moiety is selected from the group consisting of self-assembly-monomolecular (SAM) layer, one or more extracellular matrix components, a protein, a polymer layer, and a charged group. Support may be found in paragraph [00182], which recites in part,

> "Any suitable cell-adhesion promotion moieties, such as a self-assembly-monomolecular (SAM) layer (*e.g.*, alkanethiolates on gold and alkylsiloxanes on SiO_2 or SiOx,), a protein (*e.g.*, fibronectin, gelatin, collagen, laminin, proteins that promotes specific or non-specific cell attachment to the electrode or electrode array surface area), a peptide (*e.g.*, poly-L-lysine), a polymer layer and a charged group, can be used in the present apparatuses."

Further support may be found in paragraph [00119], which recites in part, "For example, a biomolecular coating can comprise an extracellular matrix component (e.g., fibronectin, collagens), or a derivative thereof, or can comprise a biochemical such as polylysine or polyornithine, which are polymeric molecules based on the naturally occurring biochemicals lysine and ornithine."

Claim 298 is newly added and provides a method for monitoring cell attachment or growth. The method includes: a) providing the device of Claim 16; attaching cells to or growing cells on the surface suitable for attachment or growth; and monitoring a change of impedance between or among the electrode structures to monitor said cell attachment or growth. Support may be found in paragraph [00241], which recites,

"In yet another aspect, the present invention is directed to a method for monitoring cell attachment or growth, which method comprises: a) providing an above-described apparatus or multi-well microplate for monitoring cell-substrate impedance; b) attaching or growing cells to or on the surface of said apparatus or in a well of said multi-well microplate; and c) monitoring impedance between or among the electrodes or electrode arrays to monitor said cell attachment or growth on said apparatus or multi-well microplate."

Claim 299 is newly added and recites the method may further include determining the amount or number of cells that are attached to or grown on the device from the monitored impedance. Support may be found in paragraph [00242], which recites in part, "For example, the present methods can further comprise determining the amount or number of cells that are attached to or grown on the apparatus or multi-well microplate from the monitored impedance.

Claim 300 is newly added and recites the method may further include deriving a cell number index from the monitored impedance. Support may be found in paragraph [00286], which recites in part, "Based on the dependent relationship between the measured impedance, cell number (more accurately, the viable cell number, or attached cell number) and cell attachment status, it is possible to derive a so-called "cell number index" (or cell index) from the measured impedance frequency spectra."

Claim 301 is newly added and provides in part, the cell number index is derived from a process selected from the group consisting of process 1, 2, 3 and 4. Process 1 including: a) at each measured frequency, calculating a resistance ratio by dividing a measured resistance when cells are attached to the electrode structure by a baseline resistance; b) determining the maximum value in the resistance ratio over a frequency spectrum; and c) subtracting one from the maximum value in the resistance ratio, wherein

a zero or near zero cell number index indicates that no cells or a very small number of cells are present on or attached to the electrode structures and an increased value of cell number index indicates that, for the same type of cells and cells under similar physiological conditions, an increased number of cells are attached to the electrode structures.

Support for process 1 may be found in paragraphs [00287]-[00288], which recite,

> "In one example, the cell number index can be calculated by: (1) at each measured frequency, calculating the resistance ratio by dividing the measured resistance (when cells are attached to the electrodes) by the baseline resistance, (2) finding or determining the maximum value in the resistance ratio over the frequency spectrum and (3) subtracting one from the maximum value in the resistance ratio.
>
> In this case, a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces. A higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces."

Newly provided process 2 includes: a) at each measured frequency, calculating the resistance ratio by dividing a measured resistance when cells are attached to the electrode structures by the baseline resistance; b) determining the maximum value in the resistance ratio over a frequency spectrum; and c) calculating a log-value of the maximum value in the resistance ratio; wherein, a zero or near-zero cell number index indicates that no cells or a very small number of cells are present on or attached to the electrode structures and an increased value of cell number index indicates that, for same type of the cells and cells under similar physiological conditions, an increased number of cells are attached to the electrode structures.

Support for process 2 may be found in paragraph [00289]-[00290], which recites,

> "In another example, the cell number index can be calculated by: (1) at each measured frequency, calculating the resistance ratio by dividing the measured resistance (when cells are attached to the electrodes) to the baseline resistance, (2)

finding or determining the maximum value in the resistance ratio over the frequency spectrum (3) and taking a log-value (e.g., based on 10 or e=2.718) of the maximum value in the resistance ratio.

In this case, a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces. A higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces."

Newly provided process 3 includes: a) at each measured frequency, calculating the reactance ratio by dividing the measured reactance when cells are attached to the electrode structures by the baseline reactance; b) determining the maximum value in the reactance ratio over a frequency spectrum; and c) subtracting one from the maximum value in the resistance ratio. A zero or near-zero cell number index indicates that no cells or a very small number of cells are present on or attached to the electrode structures and an increased value of cell number index indicates that, for same type of the cells and cells under similar physiological conditions, an increased number of cells are attached to the electrode structures.

Support for process 3 may be found in paragraph [00291]- [00292], which recites,

"In one example, the cell number index can be calculated by: (1) at each measured frequency, calculating the reactance ratio by dividing the measured reactance (when cells are attached to the electrodes) to the baseline reactance, (2) finding or determining the maximum value in the reactance ratio over the frequency spectrum (3) and subtracting one from the maximum value in the resistance ratio.

In this case, a zero or near-zero "cell number index" indicates that no cells or very small number of cells are present on or attached to the electrode surfaces. A higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrode surfaces."

Newly provide process 4 includes a) at each measured frequency, calculating the resistance ratio by dividing the measured resistance when cells are attached to the electrode structures by the baseline resistance; b) calculating the relative change in resistance of each measured frequency by subtracting one from the resistance ratio; and c) integrating all the relative-change values. The cell-number index is derived based on multiple-frequency points, and further wherein a zero or near-zero cell number index indicates that no cells or a very small number of cells are present on the electrodes and an increased value of cell number index indicates that, for same type of the cells and cells under similar physiological conditions, an increased number of cells are attached to the electrode structures.

Support for process 4 may be found in paragraph [00293] – [00294], which recites,

> "In yet another example, the index can be calculated by: (1) at each measured frequency, calculating the resistance ratio by dividing the measured resistance (when cells are attached to the electrodes) to the baseline resistance, (2) then calculating the relative change in resistance in each measured frequency by subtracting one from the resistance ratio, (3) then integrating all the relative-change value.
>
> In this case, "cell-number index" is derived based on multiple-frequency points, instead of single peak-frequency like above examples. Again, a zero or near-zero "cell number index" indicates that on cells are present on the electrodes. A higher value of "cell number index" indicates that, for same type of the cells and cells under similar physiological conditions, more cells are attached to the electrodes."

Claim 302 is newly added and provides the cell attachment or growth is monitored on a real time basis. Support may be found in paragraph [0082], which recites, "Figure **28** illustrates real time monitoring of NIH 3T3 and PAE cell proliferation using the electrode structures of 3C and 3B geometry." Further support may be found in paragraph [00234], which recites, "Preferably, a system of the present invention also includes a computer having software programs that can enable real-time measurement or

monitoring of impedance between the electrodes or electrode structures of the apparatuses of the present invention."

Claim 303 is newly provided and includes cell attachment or growth is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates attachment or growth of the cells. Support may be found in paragraph [00243], which recites in part,

> "The present methods can be used to determine whether a test compound can modulate, *i.e.*, increase or decrease, cell attachment or growth, or to screen for such a modulator. For example, the present methods can be conducted wherein the cell attachment or growth is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates attachment or growth of the cells."

Claim 304 is newly added and includes cell attachment or growth is stimulated by a growth factor and the method is used to screen the test compound for a growth factor antagonist. Support may be found in paragraph [00244], which recites in part, "In another example, the present methods can be conducted wherein the cell attachment or growth is stimulated by a growth factor and the method is used to screen the test compound for a growth factor antagonist."

Claim 305 is newly added and provides a method for monitoring effect of a test compound on cell attachment or growth, which method includes: a) providing a device of Claim 16; b) attaching cells to or growing cells in a plurality of containers of the device wherein each of the plurality of containers is associated with at least two electrode structures and contains substantially the same number and same type of cells and a different concentration of a test compound; and c) monitoring a change of impedance between or among the electrode structures as a function of time to monitor the effect of said test compound on cell attachment or growth. Support may be found in paragraph [00243], which recites,

> "The present methods can be used to determine whether a test compound can modulate, *i.e.*, increase or decrease, cell

> attachment or growth, or to screen for such a modulator. For example, the present methods can be conducted wherein the cell attachment or growth is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates attachment or growth of the cells. Generally, if a presence of a test compound results in increased cell attachment or growth, such a compound is considered as a cell attachment or growth stimulator. Conversely, if a presence of a test compound results in decreased cell attachment or growth, such a compound is considered as a cell attachment or growth inhibitor."

Further support may be found in paragraph [00248], which recites,

> "In yet another aspect, the present invention is directed to a method for monitoring cell attachment or growth, which method comprises: a) providing an above-described multi-well microplate; b) attaching or growing cells in a well of said multi-well microplate wherein each well contains substantially same number of same type of cells and serially different concentration of a test compound; and c) monitoring impedance between or among the electrodes or electrode arrays as a function of time to monitor the effect of said test compound on cell attachment or growth."

Claim 306 is newly added and provides the methods may further include determining whether the test compound is an antagonist to the growth of the cells. Support may be found in paragraph [00249], which recites in part, "In another embodiment, the present method can further comprise determining whether the test compound is an antagonist to the growth of the cells."

Claim 307 is newly added and provides the methods may also include determining the dose response of the test compound. Support may be found in paragraph [00249], which recites in part, "In still another embodiment, the present method can further comprise determining the dose-response curve of the test compound."

Claim 308 is newly added and provides a method for electroporating adherent cells, which method includes: a) providing a device of Claim 16 comprising a plurality of containers, at least one of the containers comprising at least two electrode structures; b) attaching or growing cells in said at least one of the containers; and c) applying electrical

voltage pulses to the electrode-structures to electroporate the membrane of the cells adhered to the bottom surface of the electrode structures of the at least one of the containers. Support may be found in paragraph [00237], which recites in part,

> "The methods for electroporating adherent cells using the present device or multi-well microplates comprise the following, (1) providing an above-described multi-well microplate, at least one well of which microplate contains electrodes or electrode structure units on the bottom surface, (2) attaching or growing cells in the electrodes-containing wells, (3) applying electrical voltages pulses to the electrodes to result in electroporation of the membrane of the cells adhered to the bottom surface of the wells."

Claim 309 is newly added and provides the electrode elements' widths are between about 0.5 times and about 10 times the size of cells used. Support may be found in paragraph [00174], which recites in part, "Preferably, an electrode element's width is between about 0.5 times and about 10 times the size (e.g., the width of an average cell when it spreads and attaches to the substrate) of cells used in an assay that uses the device."

Claim 310 is newly added and provides the gap between electrode elements of the electrode structures ranges from 0.2 time and 3 times the width of an averaged cell used. Support may be found in paragraph [00173], which recites in part, "While other gap dimensions may be used, preferably, the gap between electrode elements of the electrode structures ranges from about 0.2 times and 3 times the width of an average cell used in an assay using the device."

Response to Examiner Interview and Summary

Applicants graciously thank the Examiner for permitting a telephonic interview on November 8, 2007 and for providing an interview summary mailed November 15, 2007. In the interview and corresponding summary, the Examiner indicated that the proposed amendments appear to overcome the rejection of record involving the combination of Wolf and Caillat, but a new search and consideration based on the

proposed amendments would be required. The proposed amendments included limitations that the electrode structures are on the same plane and are used in determining a detectable change in AC electrical impedance. Additional proposals included that the gap is between electrode elements of different electrode structures.

The present submission includes the discussed limitations to independent claims 1 and 72, which include the electrode structures are on the same plane, a change in AC electrical impedance is detected and the gap is between electrode elements of different electrode structures. For completeness, Applicants address the rejections set forth in the previous Office Action in detail.

Response to Claim Rejections Under 35 U.S.C. §112

Claim 1 was rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner believes there is insufficient antecedent basis for "the electrode gap". It is unclear to the Examiner whether "electrode gap" refers to the gap formed between electrodes in different arrays or to the gap formed between electrodes in the same array.

Applicants have amended claim 1 to read, "the electrode gap between electrode elements of different electrode structure within each electrode array." Applicants respectfully request this rejection be withdrawn.

Response to Claim Rejections Under 35 U.S.C. § 103

1. Claims 1-3, 7-13, 15, 25, 26, 36, 38-40, 43, 72, 287 and 288 are not Obvious Over Wolf (US 6280586) in view of Caillat (US 6630359)

The examiner has rejected claims 1-3, 7-13, 15, 25, 26, 36, 38-40, 43, 72, 287 and 288 under 356 U.S.C. §103(a) as allegedly being obvious over Wolf in view of Caillat. Specifically, the Examiner states that with respect to claims 1, 8, 9, 36, 43, 72, 287 and 288, Wolf discloses a device for detecting cells comprising a non-conductive substrate

(Figure2:5) having two opposing ends, and a plurality of electrode arrays positioned on the substrate. Each electrode array comprises at least two electrodes (Figure 2:10), and electrically conductive traces and connection pads are in communication with the electrode arrays. The electrodes are used to detect impedance changes resulting from attachment of cells to the electrode surface. This is described in column 2, lines 39-55, column 3, lines 11-28, and column 7, lines 29-50. Column 7, line 63 to column 8, line 12 indicates that the electrodes have a surface (Figure 5:13) that is suitable for cell attachment and growth. Wolf, however does not expressly state that the electrodes in each array have a width of more than 1.5 to 15 times the width of the gap between the electrodes.

The Examiner then provides Caillat in support of a gap having a width from 1.5 to 15 times the width of an array. The Examiner argues Caillat discloses a device for detecting cells that comprises a non-conductive substrate (Figure 2:21) that accommodates a plurality of reception electrodes (Figure 2:22-24) and a plurality of counter electrodes (Figure 2:29). A biochemical layer (Figure 2:14) is applied to the surface of the reception electrodes in order to encourage the attachment of various biological particles. Solutions are added to the gap formed between the electrodes, and changes in impedance across the gap are then detected using the conductive elements. It is clear from the Figures that the width of the electrodes is between 1.5 and 15 times the width of the gap between the reception and counter electrodes. The Examiner argues the combination of Caillat and Wolf is proper because both are from the same field of endeavor regarding microelectronic cell sensor devices.

The Examiner concludes that at the time of the invention it would have been obvious to one of ordinary skill in the art to alter Wolf's device to ensure that the electrode widths were more than 1.5 and less than 15 times the non conductive material width if it was determined through trial and error that this configuration produced the best results.

Applicants' Response

Claims 1-3, 7-13, 15, 25, 26, 36, 38-40, 43, 72, 287 and 288 are not obvious over Wolf in view of Caillat prior to amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claims 2, 3, 7-13, 15, 25, 26, 36, 38-40, 43, 287 and 288 depend, to recite a) the two electrode structures are positioned on the same plane and having the substantially the same surface area, b) the electrode element width is between 1.5 to 15 times the width of the electrode gap between electrode elements of different electrode structure with each said electrode array and c) cell attachment or growth results in cellular contact with at least one of said electrode structures further resulting in a detectable change in AC electrical impedance.

With respect to claim 72, Applicants have amended claim 72 to recite the electrodes are positioned on the same side and same plane of the substrate, electrode elements and gaps between said electrode elements of different electrode structures are arranged so that there is a more than 50% probability for cells to contact an electrode element when said cells are introduced onto the device and cell attachment or growth on any of the at least two electrode structures results in a detectable change in AC electrical impedance. Provided below is a discussion of the Examiner's combination of Caillat and Wolf with respect to the present invention.

a. Caillat and Wolf are from Different Fields of Endeavor and are Not Properly Combined

With respect to the combination of Caillat and Wolf, Caillat is not within the same field of endeavor of Applicants' invention or Wolf and therefore should not be combined with Wolf in an obviousness rejection. Applicants' invention relates to a device capable of measuring or monitoring biological cell attachment or growth. In Applicants' invention, attachment or growth results in contact with an electrode, which further results in a detectable change in AC electrical impedance.

Referring to Column 9, lines 33-55, Wolf utilizes a measuring device for measuring physical parameters including a plurality of sensors including at least one

reference sensor and at least one electrical sensor. A measurement structure of the electrical sensor is connected to at least one function-specific plant or animal receptor cell. Provided between the receptor cell and the measurement structure is a structured biocompatible microporous interlayer to which the receptor cells at least partially adhere. The measurement structure of the reference sensor is free of connections to function-specific receptor cells. Thus, only the electrical sensor (and not the reference sensor) detects physical parameters in Wolf.

Importantly, Caillat is not a microelectronic cell sensor device for measuring or sensing biological cells using electrodes but instead involves a system for the copolymerization of monomers and reagents through the application of a DC electrical system. Caillat is about the "in situ synthesis of nucleic probes using a chemical process." (Col. 6, ll. 31-33) More specifically, Caillat includes "a process to produce a chemical or biological analysis multi-point micro-system" (Col. 3, ll. 13-15) and " a chemical or biological analysis multi-point micro-system". The system comprises "micro-wells, each micro-well being intended to receive a reagent with a conductive polymer, each micro-well comprising a reception electrode on which the reagent is fixed by means of the conductive polymer with which it is coupled …" (Col. 3, ll. 39-43). Thus the Caillat system is used for fixing reagents to reception electrodes inside the micro-wells through electrochemical method "by applying an appropriate" DC " electrical field supplied by a voltage generator" (Col. 5, ll.24-25) and not for the detection of whole cells. "A large number of reagents may be easily introduced since the copolymerization and fixation operation is collective. The monomers may be coupled with numerous types of chemical and biological substances (glucose oxidase, antigens, DNA probes, etc)." (Col. 6, ll. 25-30). Although Caillat utilizes components (glucose oxidase, antigens, DNA probes, etc) of biological systems, Caillat does not detect whole cells.

Although the Caillat system does use an electronic device to copolyermize monomers and reagants, the Caillat system does not disclose a system for the measurement or monitoring of attachment or growth of biological cells. Thus, one skilled in the art to which the present invention belongs would not consider combining

the technology of Caillat to adapt the technology of Wolf, and it would be improper to utilized Caillat and Wolf in a rejection under 35 U.S.C. §103.

b. <u>The Positioning of the Electrodes in Caillat is Not Planar and the Surface Areas of the Caillat's Electrodes are Not Substantially the Same.</u>

Claim 1 has been amended to clarify Applicants' invention, which specifically recites the electrode structures are on the same plane and have substantially the same surface area. One skilled in the art would not find it obvious to obtain these features given the presence of Caillat and Wolf.

Caillat utilizes counter electrodes and reception electrodes that are not on the same plane. More specifically referring to FIG. 1, the counter electrode 29 being vertically above the reception electrodes 22, 23, 24. The nonplanar configuration of Caillat is utilized for the electrochemical principle of copolymerizing monomers and reagents of interest and not for the microelectronic measurement or sensing of biological cells. Thus any consideration by one skilled in the art with respect to Caillat's electrode positioning would require adjusting electrodes vertically and not horizontally. Again, viewing FIG. 1, the counter electrode 29 is not spaced horizontally from the reception electrodes 22, 23, 24.

With respect to the relative surface areas of the electrodes, it is apparent that the counter electrode in Caillat has a much larger surface area than the reception electrode. Again viewing FIG 1, the counter electrode 29 is much larger than the reception electrodes 22, 23, 24. Thus, Callait does not demonstrate an electrode configuration wherein the electrodes are on the same plane and does not demonstrate the two electrodes having substantially the same surface area.

In Applicants' invention, the areas of the electrodes are substantially the same and the electrodes are positioned on the same plane. These features permit the detection of changes in impedance upon cellular attachment or growth on any of the electrodes. This is evident in the requirement of claim 1, which provides attachment or growth results in cellular contact with at least one of the electrode structures further resulting in a detectable change in AC electrical impedance between or among the electrode structures.

c. The Gap Disclosed in Caillat is Significantly Different than Applicants' Gap and Does Not Support Altering Wolf's Gap Width by One Skilled in the Art of the Present Invention

The gap in Caillat is significantly different from the gap in Applicants' invention and is significantly different from the gap in Wolf, which is indicative of the different applications. Again, Applicants' invention includes an electrode element width that is 1.5 to 15 times the width of the electrode gap between electrode elements of different electrode structure of each electrode array.

The gap in Caillat provides a different function than the gap in Applicants' invention and has different features. These different features render Applicants' invention nonobvious over Caillat. In Caillat, the gap between the reception electrode (see FIG 1: 22, 23, 24) and the counter electrode (see FIG. 1: 29) relies on the existence of the "insulating material" layer (see FIG. 1: 25), which vertically positions the electrodes. Thus the vertical positioning of the electrode elements via the insulating material forms the gap of which the Examiner relies. However, unlike the present invention, the gap in Caillat positions the counter electrode vertically above the reference electrode and does not provide a horizontal gap between electrodes. This vertical gap is important to the Caillat system for forming "micro-wells" (Col. 3, ll37-40), whereas in Applicants' invention the electrodes are planar and are spaced horizonally for detecting or monitoring electrode impedance. Thus, without the insulating material layer, there is no gap in the Caillat system. Moreover, the gap of the present invention is designed with respect to electrode width, and the gap formed by the insulating material in Caillat is not described as engineered with respect to electrode width but instead, the vertical gap formed by insulating material is essential for the formation of "micro-wells" with "sloping sides" (Col. 4, ll. 61-63). Micro-wells are important in the Caillat system since "microwells prevent the mixture of different solutions." (Col. 5, ll. 18-20). In essence, without the vertical gap or without insulating layer, there would not be microwells and the counter electrodes would collapse to the reception electrodes and the Caillat system

will not work. However, Applicants system does not utilize such an insulating layer and does not have such vertical gap.

The Examiner has acknowledged Wolf does not expressly state that the electrodes in each array have a width of more than 1.5 to 15 times the width of the gap between the electrodes.

Now referring to a combination of Caillat and Wolf, even if the two systems were designed for monitoring impedance of biological cells, which Caillat does not, Caillat would suggest to one skilled in the art to raise or lower electrodes with respect to each other and would not demonstrate adjusting the horizontal spacing. Referring again to Caillat, the electrodes are separated vertically and are not separated horizontally. Raising and lowering the electrodes would likely occur via the presence of an insulating material. Wolf provides no such insulating material and the raising or lowering Wolf's electrodes would not provide Applicants' invention.

In addition, the Caillat system operates via DC (direct current) (Col. 2, ll. 40-42, "The selected site is polarized and copolymerization is performed (at least one minute at a voltage less than 1 V)"; Col. 5, ll. 24-25, "By applying an appropriate electric filed supplied by a voltage generator ..") whereas Wolf measures "impedance or capacitance changes of the cell membranes" (Col. 4, ll.17-18) and operates inherently via AC (alternating current). Thus Caillat's electrode design would not logically apply to Wolf's. In Caillat, DC voltage is provided for the copolymerization of monomers and reagents. Importantly, the Caillat DC system can not be adapted for use with an AC system for sensing cells because the vertical difference between the reception electrode and counter electrode would create a complex and very uneven electrical field, with the strongest electrical field generated along the slope of the "insulating material layer." This complex electrical field distribution would not be suited for sensitive monitoring or sensing of cells. Thus any adaptation of the Wolf system with Caillat's gap would result in vertical manipulation of the electrodes via the gap and would result in a complex and potentially uneven electrical field. Again, the counter electrode is not horizontally spaced from the reception electrode in Caillat.

In contrast, Applicants' invention includes a gap between the electrode structures on a same plane for the measuring or monitoring the attachment or growth of biological

cells. Unlike Caillat and Wolf, the gap in Applicants' invention has been specifically engineered with relation to the widths of the electrodes to provide a system that can detect attachment or cellular growth on the surface.

Applicants' development of the present system included more than routine optimization or the incorporation of known technologies. Many scientific hurdles were encountered and the solutions to which reached far beyond what would be expected by one skilled in art with respect to a determination of obviousness. Referring to paragraphs [00173], extensive consideration was required with respect to cell size and gap between electrode elements,

> "For monitoring the behavior of cells, preferably, the gap between electrode elements does not substantially exceed the size (e.g. width of cells when they spread and attach on the substrate) of cells whose behavior is to be monitored using the device. This reduces the possibility that contact between a cell and a substrate occurs without the cell contacting at least a portion of an electrode or electrode element. Further, the width of the gap between electrode elements (or the gap size) preferably is not substantially less than the size of cells (e.g. width of an average cell when it spreads and attaches to the substrate) whose behavior is to be monitored using the device, to reduce the possibility of a cell contacting two neighboring electrode elements is measured and thereby giving rise to a somewhat disproportionately large impedance signal, in comparison to a cell contacting only one electrode element. This is particularly important, if the electrode width is much larger (e.g. ten times) than the size of cells whose behavior is to be monitored using the device. On the other hand, if the electrode width is in comparable with the size of cells (e.g. width of an average cell when it spreads and attaches to the substrate), the width of the gap between electrode elements can be somewhat smaller than the size of cells. While other gap dimensions may be used, preferably, the gap between electrode elements of the electrode structures ranges from about 0.2 times and 3 times the width of an average cell used in an assay using the device. Preferably, the width of a gap between electrodes or electrode elements of a device of the present invention used for monitoring eukaryotic cells, such as mammalian cells, such as cancer cells, endothelial or epithelial cells, is between about 3 microns and 80 microns,

> more preferably between about 5 microns and 50 microns, and most preferably between about 8 microns and 30 microns."

In addition to cell size and gap between electrode elements, the inventors of the present invention were required to consider the width of electrode elements in a system where there is no counter electrode. Unlike Caillat, the present invention does not use a counter electrode system but instead each of the electrodes may be used to monitor impedance. Thus further development was required to address the considerations of width of electrode elements . Some of the considerations of width of electrode elements in relationship to the electrode resistance in the array and in relationship to cell size were discussed in paragraph [00174], which recites,

> "The width of an electrode element is preferably not too narrow since the resistance of the electrode elements will increase as the width of the electrode element decreases. The increased resistance along the electrode elements will cause a large electrical potential difference between different points along the electrode element, resulting in difference impedance signals for cells landed on and attach to different regions of the electrode elements. It is preferred that cells landed on and attached to any region on the substrate surfaces give similar impedance signals. Thus, for an electrode element that is part of an interdigitated electrode structure or concentric electrode structure, where the device is to be used for monitoring eukaryotic cells, such as mammalian cells, such as cancer cells, endothelial or epithelial cells, the electrode width is preferably greater than about 3 microns, and more preferably greater than about 10 microns. The width is also limited by the consideration that if an electrode element is very wide, a cell that is positioned over a central part of such a very wide electrode will result in a small impedance signal when compared with that of a cell that is positioned over the edge of an electrode, where the field strength can be significantly higher. Preferably, an electrode element's width is between about 0.5 times and about 10 times the size (e.g., the width of an average cell when it spreads and attaches to the substrate) of cells used in an assay that uses the device. Preferably, for an electrode element that is part of an IDES or CCES, where the device is to be used for monitoring eukaryotic cells, such as mammalian cells, such as cancer cells, endothelial or epithelial cells, an electrode

> or electrode element is less than about 500 microns wide, and is preferably less than about 250 microns wide. In some preferred embodiments of the present invention, an electrode element is between about 20 microns and about 250 microns wide."

Thus, extensive experimentation was performed to determined gap to electrode width ratios that could be used in the counter electrode free system. Paragraph [00175] provides examples of ranges that were appropriate for the present system,

> "In the present application, it is preferred that the electrode gap between electrode elements should be designed with respect to the electrode width. ..... Preferably, the electrode element width is between 1.5 and 15 times the gap width. More preferably, the electrode element width is between 2 and 6 times the gap width; for example, if the electrode width is 90 microns at the widest point of each electrode, the gap width would be about 20 microns at the widest point of the gap between adjacent electrodes. For the present application, the electrode width can range from less than 5 microns to more than 10 mm. Preferably, the electrode width is in the range between 10 micron and 1 mm. More preferably, the electrode width is in the range between 20 micron and 500 micron."

There were technical difficulties beyond manipulation and design of the electrode array itself, but also in electrically connecting the array. Examples are discussed in paragraph [00176], which recites,

> "Thus, such connection traces may have an electrically insulating coating so that molecular reactions on or cell attachment to these connection trace regions will not result in a change in impedance between or among electrodes. In some embodiments, the electrode buses or electrically-conducting connection traces (e.g., 125 and 225 in Figure **1A** and **1B**) to connect the electrode elements may be located outside the bottom surface of a fluidic container or well that comprise the electrode structure. In this way, when sample solutions are added into the fluidic container or well, molecular reactions (or cell attachment) will not occur on such electrical connection traces. Taking the electrode structure 110 in **Figure 1A** as an example, the inner diameter of the arc-shaped, electrically conducting connection traces may have a diameter of 1.2 mm. This

> exemplary device is assembled to a plastic, cylinder shaped, fluidic container which has openings on both ends. The inner diameter of the cylinder-shaped fluidic container may be 1 mm. Using a double-sided adhesive (for example, a pressure-sensitive-adhesive), the electrode device can be bond to the fluidic container. The electrode area is concentrically aligned with and bond to a circular end of the fluidic container. Thus, the 1.2 mm diameter will be located outside of the bottom surface of the container."

Another example is discussed in paragraph [00204], which recites,

> "Electronic connection from such multi-well plates to external impedance analyzer present a significant challenge because of limited space on the bottom side of these plates. The electrode structures are facing upwards in operation. In one exemplary embodiment for connecting electrode structures to external impedance analyzers, the electronic connection pads are located at the ends of the electrode-containing substrates (see, for example, **Figure 12A** and **12B**). Because of very limited spaces available along the bottom edges of the multi-well plate, connectors used in the electronics industry cannot be directly used to such devices. In addition, because of the frame of the multi-well plate, there may not be space available for electronic connections from the top side to the connection pads at the ends of the electrode-containing substrates. For this reason, specific design is required for connecting the up-facing the connection pads to become bottom-facing. In one approach, a small PCB board (see **Figure 13A**) with straight-line conductor lines is down-facing and one end of all the conductor lines is conductively-bonded to the connection pads (see Figure **13B** and **13C**). Then the other end of the conductor lines can be accessed from the bottom. container."

Thus, the development of Applicants' invention required more than routine experimentation in view of one skilled in the art. Applicants were required to traverse many technical hurdles that did not have obvious answers. Clearly Caillat and Wolf did not require extensive consideration of proper gap to electrode width ratios. This was in part because both Wolf and Caillat operate differently than Applicants' invention.

For completeness, Applicants also address the Examiner's argument that Caillat implies that is known in the art to consider a variety of width sizes in order to produce the

best configuration because Caillat indicates electrode width and gap sizes all depend on several considerations that involve engineering tradeoffs. There is no mention in Caillat of requirements of gap width with respect to electrode width. Thus there is no discussion provided to address whether electrode width or gap should be altered in relationship to each other to achieve the desired results. Indeed, for electrochemical work in Caillat, such as for the copolymerization of monomers and reagents, the key is the voltage applied to the electrode being appropriate magnitude so that electrochemical copolymerization can occur on the reception electrode (Col. 5, ll. 24-26). Thus, there is no need to alter the geometry of electrode width or electrode gap in Caillat. Although Caillat does mention the height of the insulating material layer is between 1 micron and 50 microns, this is likely related to the need of making micro-wells on the same structure and is not for engineering tradeoffs related to electrode width and gap.

In view of the above technical hurdles that Applicants were required to overcome, neither Caillat nor Wolf provides solutions or considers the difficulties in the development of Applicants' technology and thus could not be relied upon by one skilled in the art to find the present invention obvious.

d. <u>Caillat Does Not Monitor Cell Attachment or Growth; It Is Unclear Whether Attachment or Growth of Biological Cells in Caillat Would Result in Detectable Change in Impedance and Detection Using Wolf Requires Attachment to a Microporous Interlayer That is in Contact with an Electrical Sensor</u>

For clarity, Applicants' have amended claim 1 to recite cell attachment or growth results in cellular contact with at least one of the electrode structures resulting in a detectable change in AC electrical impedance.

The Caillat system does not provide surface for cell attachment or growth where such attachment or growth results in cellular contact with at least one of the electrode structures further resulting in a detectable change in AC electrical impedance. As discussed above, the Caillat system is for the copolymerization of monomers and

reagents. The Caillat system is not for the monitoring or cells and thus Caillat does not describe the attachment or growth of biological cells.

In addition, it is unclear that had cells been added to Caillat system, whether attachment of cells on Caillat would result in a detectable change in AC electrical impedance. First, as mentioned above, the Caillat system copolymerizes monomers with reagents using a DC system whereas the present invention utilizes an AC system to measure or detect changes in biological cell growth or attachment. Therefore the Caillat system is not designed for measuring AC electrical impedance to monitor cells. "Micro-wells" are used in Caillat to "prevent the mixture of different solutions". Within each micro-well, there is one and only reception electrode on the bottom. Had cells been added to each of such micro-wells, cells would very-be likely settled to only the bottom reception electrode. This is completely different in Applicants invention where each electrode array comprises at least two electrode structures on the same plane and each electrode structure comprises at least two electrode elements. Cells have same likelihood to land on either electrode structure. Second, even if the Caillat system were adapted for use with an AC system, if cells were added to the Caillat system, there is no indication that a change in AC electrical impedance could be detected. Because of the requirement that there be an insulating layer and the gap in Caillat requires the counter electrode to be positioned above the reception electrode, the electrical field would be unevenly distributed across the system. In such a system the electrical field would be strongest along the slopes where the reception electrode is in closest proximity to the counter electrode. Thus it would be unclear whether such complex electrical field distribution is suited for monitoring cells and whether any detectable change in impedance would actually occur in such a system. Therefore it is unclear whether attachment or growth of cells on Caillat would result in detectable change in impedance.

With respect to Wolf's structured microporous interlayer, In Wolf's sensor design,

> "The object is accomplished in that provided between the receptor cells and /or the target cells and the measurement structure is a structured, microporous interlayer which the target cells and/or receptor cells accept as neighbor for adherence." Col 2, ln. 15-18. "... wherein provided between the receptor cells and the measurement structure

(6) is a structured, biocompatible microporous interlaye (13) ...." Col. 9, ll. 47-49 in Claim 1. "The interlayer provided is in particular a marcromolecular porous layer which on the one hand induced adhesion of the cells and on the other hand is proportional in the pores size so as to be permeable for certain ions, molecules or cell areas. By way of example, an SiO2 layer sputtered or applied to the measurement structure, an Al2O3 layer or a Ta2O5 layer can also be provided as the interlayer. By means of the structured interlayer, the electronic measurement structure is conditioned in such a way the target cells or receptor cells accept the measurement structure as neighbour and become better adhere to it. The porosity of the interlayer allows that the ions, molecules or cell areas to be measured of the target cells or receptor cells can reach electrically active areas of the measurement structures." Col. 2, ln 64-Col. 3, ln 30).

The structured, porous interlayer between the cells and the electrode sensor surfaces is a very important difference between Wolf's sensor design and Applicants' electrode design. In Applicants' invention there is no requirement for such structured, porous interlayer and cells are directly in contact with electrode structures. Indeed, had Applicants' design been altered to include such features used in Wolf, the "structured, porous interlayer" would significantly affect the impedance measurements.

With respect to claims 2, 3, 7-13, 15, 25, 26, 36, 38-40, 43 and 287-289, these claims depend from claim 1. Thus the arguments with respect to claim 1 are incorporated herein by reference in their entirety.

With respect to claim 72, Applicants have amended claim 72 to recite the electrodes are positioned on the same side and same plane of the substrate, electrode elements and gaps between said electrode elements are arranged so that there is a more than 50% probability for cells to contact an electrode element when said cells are introduced onto the device and cell attachment or growth on any of the at least two electrode structures results in a detectable change in AC electrical impedance between or among the electrode structures. Applicants also amend claim 72 to recite the gap is between electrode elements of different electrode structures.

Applicants incorporate herein the arguments above with respect to Caillat does not include the electrodes being on the same plane of the substrate. In addition, as described above neither Caillat nor Wolf provide that cell attachment or growth on any of the at least two electrode structures results in a detectable change in AC electrical impedance. More specifically, Caillat is utilized for copolymerization of monomers and reagents and Wolf requires cell attachment to a microporous interlayer, which only affects the electrical sensor and not the reference sensor.

2. Claims 4, 16-24, 29-32, 34, 44, 47-50 and 289 are not Obvious Over Wolf (US 6280586) in view of Caillat (US 6630359) and further in view of Wolf (US 6376233)

The Examiner has rejected claims 4, 16-24, 29-32, 34, 44, 47-50 and 289 as allegedly being obvious over Wolf in view of Caillat and further in view of Wolf.

Applicants have amended claim 1, from which claims 4, 16-24, 29-32, 34, 44, 47-50 and 289 depend. Wolf 6376233 does not cure the deficiencies in a proper obviousness rejection over Wolf 6280586 in view of Caillat. Thus claims 4, 16-24, 29-32, 34, 44, 47-50 and 289 are also not obvious over Wolf in view of Caillat and further in view of Wolf.

Thus, Applicants respectfully request the rejection be withdrawn and the claims allowed.

3. Claim 35 is Not Obvious Over Wolf (US 6280586) in view of Caillat (US 6630359) as applied to claim 1, and further in view of Surridge (US20030116447)

The Examiner has rejected claim 35 as allegedly being obvious over Wolf in view of Caillat and further in view of Surridge (US20030116447).

Applicants have amended claim 1, from which claim 35 depends. Surridge does not cure the deficiencies in a proper obviousness rejection over Wolf in view of Caillat. Thus claim 35 is not obvious over Wolf in view of Caillat and further in view of Surridge.

Thus, Applicants respectfully request the rejection be withdrawn and the claim 35 allowed.

4. Claim 37 is Not Obvious Over Wolf (US 6280586) in view of Caillat (US 6630359) as applied to claim 1, and further in view of Gomez (US 20030157587)

The Examiner has rejected claim 37 as allegedly being obvious over Wolf in view of Caillat and further in view of Gomez

Applicants have amended claim 1, from which claim 37 depends. Gomez does not cure the deficiencies in a proper obviousness rejection over Wolf in view of Caillat with respect to claim 1. Thus claim 37 is not obvious over Wolf in view of Caillat and further in view of Gomez.

Thus, Applicants respectfully request the rejection be withdrawn and the claim 37 allowed.

5. Claims 41 and 42 are not obvious over Wolf (US 6280586) in view of Caillat (US 6630359) as applied to claim 40, and further in view of Sugihara (US 6132683)

The Examiner has rejected claims 41 and 42 as allegedly being obvious over Wolf in view of Caillat and further in view of Sugihara.

Applicants have amended claim 1, from which claim 41 and 42 depend. Sugihara does not cure the deficiencies in a proper obviousness rejection over Wolf in view of Caillat with respect to claim 1. Thus claim 41 and 42 is not obvious over Wolf in view of Caillat and further in view of Sugihara.

Thus, Applicants respectfully request the rejection be withdrawn and the claims 41 and 42 allowed.

Response to Double Patenting Rejections

1. The Examiner has issued a provisional obviousness-type double patenting rejection of claims 1, 4, 25, 38-40 and 72 over copending Application No. 11/055,639 in view of Caillat (US 6630359).

Applicants have amended claim 1 to recite a) the two electrode structures are positioned on the same plane and having the substantially the same surface area, b) the electrode element width is between 1.5 to 15 times the width of the electrode gap between electrode elements of different electrode structure with each said electrode array and c) cell attachment or growth results in cellular contact with at least one of said electrode structures further resulting in a detectable change in AC electrical impedance.

Applicants have amended claim 72 to recite a) a non-conducting substrate; b) at least two electrode structures fabricated to the same side and plane of said substrate, wherein: i) each of said at least two electrode structures has at least two electrode elements; and ii) said at least two electrode structures have substantially same surface area; iii) said electrode elements and gaps between said electrode elements of different electrode structures are arranged so that there is a more than 50% probability for cells to contact an electrode element when said cells are introduced onto said device; and c) at least two connection pads located on said substrate, wherein said device has a surface suitable for cell attachment or growth and said cell attachment or growth on any of said at least two electrode structures results in detectable change in AC electrical impedance between or among said electrode elements.

Application no. 11/055,639 in view of Caillat does not recite the combination of all of these elements and thus Applicants respectfully request the provisional double patenting rejection be withdrawn.

2. The Examiner has issued a provisional obviousness-type double patenting rejection of claims 1, 4, 25, 38-40 and 72 over copending Application No. 10/987,732 in view of Caillat (US 6630359).

Applicants have amended claim 1 to recite a) the two electrode structures are positioned on the same plane and having the substantially the same surface area, b) the electrode element width is between 1.5 to 15 times the width of the electrode gap between electrode elements of different electrode structure with each said electrode array and c) cell attachment or growth results in cellular contact with at least one of said electrode structures further resulting in a detectable change in AC electrical impedance.

Applicants have amended claim 72 to recite a) a non-conducting substrate; b) at least two electrode structures fabricated to the same side and plane of said substrate, wherein: i) each of said at least two electrode structures has at least two electrode elements; and ii) said at least two electrode structures have substantially same surface area; iii) said electrode elements and gaps between said electrode elements of different electrode structures are arranged so that there is a more than 50% probability for cells to contact an electrode element when said cells are introduced onto said device; and c) at least two connection pads located on said substrate, wherein said device has a surface suitable for cell attachment or growth and said cell attachment or growth on any of said at least two electrode structures results in detectable change in AC electrical impedance between or among said electrode elements.

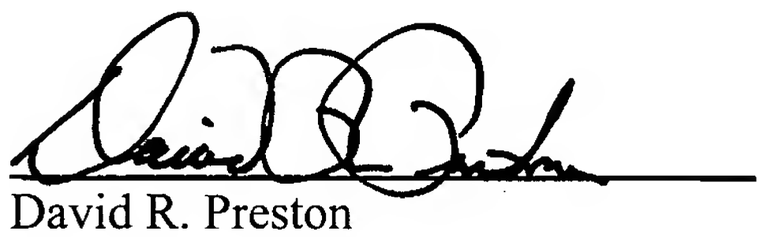
Application no. 10/987,732 in view of Caillat does not recite the combination of all of these elements and thus Applicants respectfully requests the provisional double patenting rejection be withdrawn.

Conclusion

In view of the amendments and argument set forth above, Applicants respectfully request all rejections be withdrawn and a notice of allowance be issued in this case.

Respectfully submitted,

Date: Dec. 13, 2007



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